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Jumping translocations of 1q in donor cell-derived myelodysplastic syndrome after cord blood transplantation: Case report and review of the literature

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Abstract. Donor cell-derived leukemia and myelodysplastic syndrome (DCL) is a rare complication in patients after allogenic stem cell transplantation (SCT). Since 1971, numerous cases of DCL have been reported, but the detailed mechanisms of DCL are still unclear. A patient with jumping translocations (JTs) of 1q in umbilical cord blood donor cell-derived myelodysplastic syndrome (MDS), which likely occurred due to genetic alterations of *TET2* and *ASXL1* after cord blood transplantation (CBT), was examined in this study. Previously reported DCL cases after CBT that focused on the cytogenetic and molecular characteristics of these patients and patient outcome were reviewed. A total of 30 cases of DCL after CBT were identified between 2005 and 2018. The median time from CBT to the development of DCL was 16 months. The number of patients with DCL who were diagnosed with acute myeloid leukemia (AML) and MDS was 19 and 8, respectively. JTs were frequently observed in 5 of 27 DCL patients who had cytogenetic abnormalities, including our patient. Molecular abnormalities were described in 7 of the cases, and the most frequent abnormality was an *NPM1* mutation. Other gene mutations that were usually found in *de novo* MDS or AML were observed in JT-DCL after CBT. From these results, chromosomal abnormalities such as JTs that occur subsequent to genetic alterations were seemed an important mechanisms underlying DCL onset in patients after CBT. Further molecular analyses regarding the genetic alterations of JTs are required to understand the pathogenesis of umbilical cord blood-derived JT-DCL.

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Introduction

Donor cell-derived leukemia and myelodysplastic syndrome (DCL) is a rare but crucial complication in patients after allogenic stem cell transplantation (SCT). Since the first report of DCL was published in 1971, numerous cases of DCL have been reported (1-9). Previous cases of DCL have been reported with all stem cell sources, including peripheral blood stem cells (2,9,10), bone marrow (2,9,11), and umbilical cord blood (5,9,12-14). Umbilical cord blood is recognized as an alternative stem cell source for transplantation, and since 2005, some cases of DCL after cord blood transplantation (CBT) have been reported to have poor prognoses (12-15).

Possible mechanisms for DCL that have been explored include preleukemic clones already present in the graft at the time of transplantation (7,8,16), telomere shortening in engrafted donor cells (17), the effects of residual agents of conditioning chemotherapy or radiation on infused graft cells and/or stromal elements (18), and recipient stromal cells that may drive the development of malignancy and impaired immune surveillance in the posttransplantation period (7). However, the detailed mechanisms of DCL are still unclear, and if we can clarify the mechanism of umbilical cord blood stem cell-derived leukemia, it may explain the mechanism of leukemogenesis. Recently, some reports of genetic alterations in DCL by whole genome or target sequencing have been published (19). These results suggest that some DCL cases develop due to an accumulation of the same genetic mutations as *de novo* acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). However, it is not sufficient to clarify the whole picture of genetic alterations in DCL; the accumulation of a genetic mutation profile of DCL cases is needed.

Jumping translocations (JTs) are a rare type of cytogenetic abnormality detected in various types of leukemia but infrequently in patients with MDS. JTs occur when a segment of a particular chromosome is duplicated and inserted into several

other chromosomes, resulting in multiple gains of the chromosomal segment via multiple translocations and a possible loss of segments in the recipient chromosomes (20,21). The most commonly observed JT involves 1q as the donor chromosome segment and is referred to as a JT of 1q. Previously, JT of 1q had been identified in *de novo* MDS or AML (20-22), and a few cases had been reported in DCL. The prognosis of JT of 1q is poor, and the translocation is associated with a high risk of progression to AML or treatment resistance (23,24).

Here, we report a case of JT of 1q in umbilical cord blood donor cell-derived MDS that most likely occurred due to genetic alterations after CBT. The patient achieved complete remission (CR) after treatment with azacytidine and a second CBT. Therefore, we reviewed 30 previously reported cases of DCL after CBT, and we described the cytogenetic and molecular characteristics of the patients and patient outcome.

Case report

Patient and donor. A 49-year-old female with AML without maturation (FAB M1) was treated with induction and consolidation chemotherapies, achieving CR in our hospital. Two years later, she relapsed and had bone marrow and skin lesions. The myeloblasts were positive for CD33 and CD34, and negative for B and T lymphoid lineage markers by flow cytometric analysis. Cytogenetic analysis revealed a normal female karyotype. She achieved a second CR after induction chemotherapies and consecutively underwent allogenic CBT after a reduced intensity conditioning regimen with fludarabine (25 mg/m^2/day, 5 days), cytarabine (3,000 mg/m^2/day, 4 days), melphalan (70 mg/m^2/day, 1 day) and 6 Gy of total body irradiation. Prophylaxis for graft vs. host disease (GVHD) included the use of tacrolimus until 248 days after CBT (day+248). The graft source was a female donor with human leucocyte antigen class I, A (HLA-A) and an HLA-DRB1 split-allele mismatch. Favorable hematological recovery was observed on day+28, and bone marrow examination on day+48 showed complete chimera of the donor. Acute GVHD of the skin (stage 4, grade IV) was observed on day+35 and was ameliorated by treatment with methylprednisolone. From day+277, she developed anemia that became gradually worse. Bone marrow examination on day+417 revealed normocellular marrow with 18.6% myeloblasts. Morphologic dysplasia, such as micromegakaryocyte and megaloblastoid changes in the erythroid lineage, was observed. The blasts were positive for CD7, CD13 and CD56 and negative for B and other T lymphoid lineage markers by flow cytometric analysis. Cytogenetic analysis revealed a complex karyotype including JT of 1q abnormalities: 46, XX, der(16)t(1;16)(q21;q22)ins(16;?)(q22;?) [18/20], 46, XX [2/20]. Additionally, marrow blood chimerism was analyzed by using the short tandem repeat (STR) method at day+417, and at day+441, the donor type was maintained, and the marrow HLA was the donor type. According to these results, the patient was diagnosed with JT of 1q in donor cell-derived MDS with excess blasts.

CD34-positive cell collection and DNA extraction. We collected CD34-positive cells from the marrow of DCL patients before treatment. Mononuclear cells were separated from 4 ml of marrow by differential centrifugation over a Ficoll-Paque PLUS gradient (GE Healthcare Biosciences), and purified CD34 cells were obtained by using the CD34 MicroBead kit UltraPure, human and MACS cell separation method (Miltenyi Biotec). DNA was extracted using the SepaGene DNA extraction kit (Sanko Junyaku).

Target sequencing for genetic mutations. We investigated driver mutations in 50 genes that were related to myeloid leukemia development in this DCL case by target gene sequencing analysis. Details of the 50 genes are described in supplementary Table SI. Over 500 ng of DNA from CD34-positive cells was sequenced by multiplex PCR using GeneRead DNAseq Targeted Panels V2 [Human Myeloid Neoplasms (NGHS-003X)] (QIAGEN) according to the manufacturer's instructions. The DNA was sequenced using MiSeq (Illumina) with Reagent kit V2 in 151-base-pair (bp) paired-end reads. The average read depth of coverage was 1,500x to allow for the detection of rare mutations and to accurately estimate variant allele frequencies (VAFs).

This analysis was approved by the Ethics Committee of Kawasaki Medical School (IRB no. 2408) (Kurashiki, China), and the patient provided written informed consent.

Variant data analysis. Alignment and variant calling were performed using the GeneRead targeted enrichment panel variant calling web service (http://ngsdataanalysis.sabiosciences.com). Original FASTQ files generated by MiSeq were uploaded into the web service, and then, we chose somatic workflow of the paired-end read mode. The workflow performed a variant filtering to reduce false positive variant calls. Single-nucleotide variants (SNVs) with <4% VAF, as well as insertions and deletions (indels) with <20% VAF, were removed. Functional annotations of the Ensembl database GRCh37.75 (25) and the possible effects of variants were added using SnpEff version 4.0E (26). Using these annotations, the workflow-passing variants were filtered first for those that were predicted to alter amino acid sequences (missense, nonsense, and splice-site mutations and indels in coding regions) and then for those that were rare [<1.0% minor allele frequencies (MAF) in the HapMap-JPT (Japanese in Tokyo, Japan), the 1,000 Genomes EAS (the East Asian population including 104 Japanese individuals) or the Human Genetic Variation Database (HGVD, http://www.genome.med.kyoto-u.ac.jp/SnpDB/), which contained genetic variations determined by whole exome sequences (WES) in 1,208 Japanese individuals]. Target sequencing and data analysis were performed by Riken Genesis Co., Ltd.

Literature review. A literature review was conducted in PubMed and the Japan Medical Abstracts Society database using the terms 'donor cell leukemia' or 'donor cell-derived leukemia' from 2005 to 2018. The papers were reviewed, and we reviewed cases of patients who developed DCL after CBT.

Results

Treatment after the development of DCL and outcomes of patients and cord blood donors. Our patient achieved CR after 3 cycles of azacytidine treatment and underwent a second allogenic CBT from an HLA-DR single-locus mismatch

male donor. The reduced intensity conditioning regimen used fludarabine (40 mg/m^2/day, 5 days), cyclophosphamide (50 mg/kg/day, 1 day) and 3 Gy of total body irradiation, and the GVHD prophylaxis included cyclosporine and mycophenolate mofetil. Favorable hematological recovery was observed on day+37, and the patient was alive 5 years after the second CBT and remained in CR.

We followed up on the prognosis of the donor, and we confirmed that the donor was healthy when she was 1 year old, but her prognosis after that time was unknown.

Mutation analysis. Target sequencing revealed that DCL cells had genetic alterations in *tet methylcytosine dioxygenase 2 (TET2)* (S1107P) and *additional sex combs like 1 (ASXL1)* (E792D), which were novel nonsynonymous mutations (Table I). Another mutation of *ASXL1* (E1028V) had never been reported in some databases but was discovered in the NCBI dbSNP database. Details of the sequence data are shown in supplementary Table SII.

Discussion

A total of 30 cases of donor cell-derived hematological malignancies after CBT were identified from 2005 to 2018 (Table II) (6,12,14,27-52). The first reports of umbilical cord blood donor-derived leukemia were published by Fraser *et al* (12) and Matsunaga *et al* (14) in 2005. Seventeen of 31 cases, including our case, were female, and the median age of the patients was 33 years (range: 1-64 years). The median time from CBT to the development of DCL was 16 months (range: 2.6-60 months). The diagnosis of DCL was AML in 19 cases, MDS in 8 cases, ALL in 2 cases, chronic myeloproliferative disorder in 1 case and T-cell large granular lymphocyte leukemia in 1 case. The outcomes were described in 22 of the cases, and the median duration following donor cell-derived hematological malignancies was 8 months (range: 7 days-70 months). Fifteen of the patients were dead, 12 patients were alive at the time the reports were written, and 4 patients were not described. Twenty-one of the patients were treated with intensive therapy, and some recent cases were treated with demethylating agents (azacitidine or decitabine) or a Janus kinase inhibitor (tofacitinib). Finally, 7 patients had a second SCT, and 4 of those patients were alive. In contrast, 5 patients were alive out of 17 patients who were treated without SCT. The results of cytogenetic analyses were described in 27 cases, and the most frequent abnormalities, which were observed in 11 patients, involved chromosome 7. JT-DCL or AML were observed in 5 patients (cases 2, 8, 15, and 25 were AML, and the present case was MDS, Table II). JT of 1q21 was only detected in 2 patients, including our patient (case 2 and the present case, Table II). Molecular abnormalities were described in 7 of the cases (cases 8, 20, 22, 25, 26, 27 and the present case, Table II). The most frequent abnormality was a *nucleophosmin 1 (NPM1)* mutation, which was observed in 3 patients. Additionally, some other gene mutations that are usually found in *de novo* MDS or AML were observed. Gene mutations were found in JT-DCL, including the rearrangement of the *myeloid/lymphoid leukemia or mixed lineage leukemia (MLL)* gene (case 8), mutations of the *Janus kinase 2 (JAK2), checkpoint kinase 2 (CHEK2), Down syndrome cell adhesion molecule (DSCAM),* and *IKAROS family zinc finger (IKZF1)* genes (case 25) and mutations of *TET2* and *ASXL1* (present case).

The incidence of DCL has been estimated to range from less than 1 to 6.6% of all transplantations (2-10), and the frequency of DCL is increasing due to the increase in the number of SCTs (15). Dietz *et al* (9) reported that the risk of DCL was similar between stem cell sources. In contrast, Kato *et al* (6) reported that the incidence of DCL after CBT was significantly higher than after transplantation from other stem cell sources. The authors assumed that the naive immune function of cord blood might influence the onset of DCL (6). Shiozaki *et al* (46) estimated that a high proliferation of cord blood cells may be sufficient for inducing replication errors or mutations in DNA. However, it is difficult to accurately estimate the incidence of DCL.

Umbilical cord blood-derived leukemia has several features that are different from other stem cell sources. Shiozaki *et al* (46) reported that, concerning the type of DCL, AML and MDS occurred more frequently after CBT, whereas AML and ALL were observed at a similar frequency after bone marrow transplantatio (BMT). In our review of DCL after CBT, AML and MDS were most frequently observed in 27 cases, but ALL was observed in only 2 cases. The median time to the development of DCL after CBT was 16 months in our reviewed cases. DCL occurred more quickly after CBT (14.5 months) than after BMT (36 months), and the timing was similar to the period in which infant leukemia occurs with the highest incidence (46). The prognosis of DCL is generally poor, and 15 of 27 patients died of DCL progression or complications accompanying treatment. The median duration of follow-up in 22 cases of DCL after CBT was 8 months. The survival ratio of DCL patients who were not treated with SCT was lower than that of patients who were treated with SCT (5/17 patients, 29% vs. 4/7 patients, 57%, respectively). Our present patient is in CR 5 years after the second SCT, which is the longest surviving case in our reviewed reports. SCT seems to be an effective treatment for patients with DCL after CBT. Recently, DCL patients who were treated with novel drugs, such as demethylating agents or a Janus kinase inhibitor, have been reported. Although the prognosis of DCL is poor, our case obtained long-term survival by treatment with demethylating agents and subsequent SCT. This result suggests that the prognosis of DCL may improve by treatment with demethylating agents and subsequent transplantation. Obviously, it is necessary to consider in many cases in the future.

Regarding the karyotypes of DCL after CBT, the frequency of a normal karyotype was slightly lower than that seen after BMT (46). A normal karyotype was only seen in 6 out of 27 cases in our review. These results suggest that chromosomal abnormalities may play an important role in the development of DCL after CBT. The most frequent abnormalities involved chromosome 7 (11/27 cases, 41%). Moreover, we found 5 cases with JT chromosomal abnormalities (5/27 cases, 19%). JTs are very rare cytogenetic phenomena in *de novo* leukemia and MDS; however, JT abnormalities were observed frequently in patients with DCL after CBT. As far as we investigated, the frequency of JT in other stem cell sources was lower than that of CBT. Hertenstein *et al* (3) reported 14 cases of DCL in a survey of the European Group for Blood and Marrow Transplantation

Table I. Results of target sequencing in 50 genes which were related to myeloid leukemia development in patient with jumping translocations of 1q in DCL.

							Reports in data bases			
Gene locus	DNA change	Protein change	Reading number	Gene	VAF	db SNP rs ID	1,000	HGVD	HEP8	COSM
chr4:106158418	T>C	p.S1107P	1,007	TET2	0.058					
chr4:106196951	A>G	p.I1762V	674	TET2	0.994	rs2454206	Y	Y	Y	
chr8:41906095	A>G	p.L134S	551	KAT6A	0.503	rs3824276	Y	Y	Y	
chr12:111884608	T>C	p.W262R	337	SH2B3	1.000	rs3184504	Y	Y	Y	
chr13:28624294	G>A	p.T227M	503	FLT3	0.992	rs1933437	Y	Y	Y	
chr17:7579472	G>C	p.P72R	148	TP53	0.986	rs1042522	Y	Y	Y	Y
chr18:42456653	G>A	p.A222T	1,531	SETBP1	0.462	rs663651	Y	Y	Y	
chr18:42532606	G>A	p.V1101I	647	SETBP1	0.530	rs3744825	Y	Y	Y	Y
chr18:42532693	C>A	p.P1130T	689	SETBP1	0.478	rs1064204	Y	Y	Y	
chr20:31022906	A>T	p.E792D	187	ASXL1	0.112					
chr20:31022959	T>C	p.L810P	390	ASXL1	0.941	rs6058694	Y	Y	Y	
chr20:31023613	A>T	p.E1028V	395	ASXL1	0.484	rs192330235				
chr20:31024207	C>T	p.S1226F	310	ASXL1	0.494	rs74638057	Y	Y		
chrX:129147079	T>C	p.F111L	314	BCORL1	0.990	rs4830173	Y	Y	Y	

Data bases; 1,000, the 1,000 Genomes the East Asian population; DCL, donor cell-derived leukemia and myelodysplastic syndrome; VAF, variant allele frequencies; HGVD, Human Genetic Variation Database; HEP8, healthy elderly persons of 8 Japanese male; COSM, COSMIC; Y, yes (indicates that the mutation is reported in the corresponding database).

Table II. Clinical features and cytogenetic abnormalities of reported cord blood donor-derived hematological neoplasms.

Author, year	Case no.	Age/sex	Primary disease	Duration following CBT (M)	Type of DCL	Treatment	Outcome	Duration following DCL (M)	Cytogenetic analysis of DCL	(Refs.)
Matsunaga *et al*, 2005	1	57/F	ATL	8.5	AML(M2)	None	Death	7days	46,XX,add(19)(p13)	(14)
Fraser *et al*, 2005	2	1/M	LCS	40	AML with TLD	Chemotherapy	Death, infection	10	46,XY,der(7)t(1;7)(q21.1;q22)	(12)
Kato *et al*, 2016	3	32/F	AML(M0)	11	AML(M2)	2nd SCT	Death, TMA	6	46,XX	(6)
Sevilla *et al*, 2006	4	4/F	AML(M5b)	2.6	MDS	None	Alive at non CR	24	45,XY,-7(80%)	(27)
Mitsui *et al*, 2007	5	41/M	B-ALL, NK/T-NHL	9	CMPD	2nd BMT	Alive	14	46,XX,t(7;11)(p15;p15)	(28)
Nagamura-Inoue *et al*, 2007	6	32/F	AML(M2)	15	AML	ND	ND	ND	ND	(29)
Iwato *et al*, 2007	7	59/F	ALL	10	AML from MDS	None	Death	1.5	46,XX	(30)
Hamaki *et al*, 2008	8	31/M	Hodgkin lymphoma	16	AML(M5a)	Chemotherapy	Death, sepsis	13	45,XX,add(4)(q31.1),der(6)t(6:7)(p23;q11.2), 45,XX,add(4)(q31.1),der(6)t(6:7)(p23;q11.2),-7,der(11)(q23)Rearrangement of the *MLL* gene(+)[a]	(31)
Konuma *et al*, 2009	9	34/M	ALL	10	MDS	2nd CBT	Death, VOD	5	46,XY,der(6q),-7	(32)
Ohnaka *et al*, 2009	10	50/M	NHL	17	AML from MDS	2nd CBT	Alive	8	ND	(33)
Castleton *et al*, 2010	11	32/F	CML	17	AML with TLD	None	Death, sepsis	1week or more	44,XY,-7,del(17),t(17;21)(p1?3;?),-21	(34)
Crow *et al* 2010	12	3/F	AML(M5a)	14	AML(M5a)	Chemotherapy	Death	ND	45,XY,-7	(35)
Shono *et al*, 2011	13	31/F	ALL(L2)	7	ALL	Chemotherapy	Alive at PR	ND	46,XX	(36)
Yoshida *et al*, 2011	14	30/F	B-ALL	8	B-ALL	ND	ND	ND	ND	(37)
Gustafsson *et al*, 2011	15	10/M	Fanconi anemia	24	AML	2nd SCT	Death, GVHD	16	46,XX,del(5)(q13q33)/46,XX, der(9)t(9;11)(q32;q3?)/46,XX	(38)
Yamazaki *et al*, 2011	16	58/F	MDS	14	MDS	Chemotherapy	Death	1	47,XY,+10,add(10)(p11.2)x2	(39)
Wang *et al*, 2011	17	55/M	Therapy-related MDS	6	MDS	None	Spontaneous remission	28	-7 in 68% of cells by FISH	(40)
Wang *et al*, 2011	18	22/F	B-ALL	5	MDS	Supportive therapy	Alive with disease	8	45,XY,-7/46,XY	(40)
Cotter *et al*, 2012	19	30/M	B-ALL	47	MDS	Chemotherapy	Alive	ND	44,XY,-3,del(4)(q23q33), der(5;17)(p10;q10),-7,t(8;22)(p21;q13)	(41)

Table II. Continued.

Author, year	Case no.	Age/sex	Primary disease	Duration following CBT (M)	Type of DCL	Treatment	Outcome	Duration following DCL (M)	Cytogenetic analysis of DCL	(Refs.)
Chonabayashi *et al*, 2012	20	48/F	T-cell lymphoma	18	AML (M5a)	2nd CBT	Alive	36	46,XX, mutation of *NPM1* and *FLT3*-ITDa	(42)
Sugimori *et al*, 2012	21	23/F	AA	27	MDS	Chemotherapy	Alive	ND	46,XX	(43)
Rodríguez-Macías *et al*, 2013	22	44/M	ALL	16	AML	Chemotherapy	Death	8	46,XX, mutation of *NPM1*[a]	(44)
Hamahata *et al*, 2013	23	26/F	ALL	41	AML	ND	ND	ND	46,XX	(45)
Shiozaki *et al*, 2014	24	52/M	AML from MDS	24	AML	Chemotherapy	Death, sepsis	12	46XX,r(7)(p10q22)	(46)
Hirsch *et al*, 2016	25	54/M	AML with maturation	20	AML	ND	ND	ND	48,XY,+6,der(13)t(13;?)(p11;?), +21/46,XY, mutations of *JAK2, CHEK2, DSCAM, IKZF1*[a]	(47)
Suárez-González *et al*, 2018	26	- /F	ALL with t(1;19)	16	AML	Chemotherapy	Alive with	83 days disease	46,XX, mutations of *POU2F2, CA9, NOTCH1, POU4F1, NRAS, FMN2, PTPN11, MAP2K1, NPM1*[a]	(48)
Ketterl *et al*, 2018	27	6/F	T-ALL	48	T-LGL	MTX, CY, Tocafitinib	Alive with disease	ND	46,XY, mutation of STAT3a	(49)
Adachi *et al*, 2018	28	64/M	AML with MRC	11	AML(M7)	Chemotherapy, azacitidine	Death	28	46,XX	(50)
Ikegawa *et al*, 2016	29	60/M	MDS	60	AML	Chemotherapy	Death, sepsis	68 days	46,XX,+1,der(1;7)(q10;q10)	(51)
Hayes *et al*, 2015	30	41/M	B-ALL	17	AML, myeloid sarcoma	Decitabine	Death, Multiorgan failure	64 days	ND	(52)
Present case	N/A	50/F	AML(M1)	34	MDS	2nd CBT	Alive at CR	70	47,XX,der(16)t(1;16)(q21;q22) ins(16;?)(q22;?), mutations of *TET2, ASXL1*[a]	N/A

[a]Molecular abnormalities. (M), months; F, female; M, male; DCL, donor cell derived hematological malignancies including leukemia, myelodysplastic syndrome and myeloproliferative neoplasms; LCS, Langerhans cell histiocytosis; AML with TLD, acute myeloid leukemia with trilineage dysplasia; ATL, adult T-cell leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CMPD, chronic myeloproliferative disorder; MDS, myelodysplastic syndrome; CR, complete remission; ND, not described; NHL, non-Hodgkin lymphoma; NK/T-NHL, natural killer/T-non-Hodgkin lymphoma; TMA, thrombotic microangiopathy; VOD, veno-occlusive disease; CML, chronic myeloid leukemia; GVHD, graft vs. host disease; AA, aplastic anemia; T-ALL, T-cell acute lymphoblastic leukemia; T-LGL, T-cell large granular lymphocyte leukemia; MTX, methotrexate; CY, cyclophosphamide; AML with MRC, acute myeloid leukemia with myelodysplasia-related changes; N/A, not applicable.

(EBMT); 12 donor sources were bone marrow and 2 were peripheral blood, but JT was not observed. Shiozaki *et al* (46) reported the results of comparing the features of DCL cases following BMT and CBT. In that report, JT was observed in 4 of 24 cases of DCL after CBT but not in 52 cases of DCL after BMT (27). From these limited results, JT abnormalities seemed to be an important mechanism underlying the development of DCL after CBT.

Recent studies revealed that several genetic mutations were found in de novo MDS or leukemia patients harboring JTs. Yeung *et al* (22) investigated genetic mutations in 6 cases of JT-MDS patients by using target gene panel next-generation sequencing. They reported that *TET2* mutations were the most frequently observed mutations in their patients (4 of 6 JT-MDS patients), and *SF3B1* and *ASXL1* mutations were found in 3 and 2 patients with JT-MDS, respectively. These mutations were the most frequently observed in *de novo* MDS patients. We found genetic mutations of *TET2* and *ASXL1* in umbilical cord blood-derived JT-MDS. *TET2* mutations have clearly been linked to myeloid dysfunction (53), clonal diseases such as MDS (54), and responsiveness to hypomethylating agents such as azacitidine or decitabine (55). Additionally, *TET2* mutation results in an unstable genomic state and, when present in association with JTs, indicates a poor prognosis (22). Additionally, the *ASXL1* mutation is associated with MDS development and disease progression (55). From these results, it was seemed that genetic alterations and subsequent additional chromosomal abnormalities such as JTs can lead to MDS, as in our present case.

In conclusion, we treated a JT-DCL patient who developed after CBT. Target sequencing analysis in our case and a review of previously reported DCL cases suggested that genetic mutations that are observed in *de novo* MDS and AML and not only chromosome 7 abnormalities but also JT chromosomal abnormalities are important for the development of DCL following CBT. The lengthy survival of our patient suggests that demethylating agents such as azacitidine and SCT may be effective as DCL treatment strategies. However, there are limited reports that analyze the molecular abnormalities and clinical features of JT-DCL. Further molecular analysis to understand the genetic alterations that cause JTs may facilitate targeted therapy for umbilical cord blood-derived JT-DCL.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

TK designed the research, acquired clinical data, analyzed genetic mutations and wrote the manuscript. TT designed the research, executed the study, analyzed the clinical data and wrote the manuscript. RS, KH, SY, HF, TH, AT, FS, HT, YM and HW acquired and analyzed the clinical data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Kawasaki Medical School (Kurashiki, Japan) and the patient provided written informed consent.

Patient consent for publication

The patient provided consent for publication of the data.

Competing interests

The authors declare that they have no competing interests.

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